REMARKS

Rejection of Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 Under 35 U.S.C. § 103(a)

Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky (U.S. Patent No.: 5,942,499; hereinafter, "Radomsky") in view of Binette *et al.* (U.S. Publication No.: 2005/0054595; hereinafter, "Binette").

The Office Action states that:

> Since [Radomsky] teaches addition of mixtures, one would have been motivated to add [REMICADE® infliximab] in addition to other bone forming agents and would have had reasonable expectation of success [in] obtaining an [improved] and better combination of treating osteoporosis or bone related treatment. The person of ordinary skill in the art would have been motivated to combine the references because both references teach combinatorial compositions comprising **anti-TNF agents or osteoporosis treating agents**. The person of ordinary skill would have reasonably expected success because the combinatorial compositions comprising bone forming agent and other active agents which help in treating osteoporosis were well known in the art at the time of the instant invention, as evidenced by the Radomsky et al. and one of skill in the art would have expected success by substituting the species of [REMICADE® infliximab] as taught by the '595 patent. (Office Action at page 4, first paragraph; underlined emphasis added).

Applicants respectfully disagree with the above reasoning for the rejection because, absent impermissible hindsight, one of ordinary skill in the art would not have been motivated to combine or modify the teachings of Radomsky and the teachings of Binette. The Office Action does not explain why one of ordinary skill in the art would have selected a monoclonal antibody such as REMICADE® infliximab in conjunction with a bone forming agent (BFA) to treat an uncoupled resorbing bone. The reasoning for the rejection is based on selectively choosing elements from distant prior art references and piecing the specific elements together in order to arrive at the present invention without providing a proper motivation to combine. Courts have warned against these types of obviousness analyses.

In the recent case *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d. 1350, 83 USPQ2d 1169 (Fed. Cir. 2007), the court stated that the test for obviousness of chemical compounds is consistent with the legal principles enunciated in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007):

> While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does in an obviousness determination. Moreover, the Court indicated that there is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis...As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry... Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound. 83 USPQ2d at 1174; emphasis added.

In *Abbott Laboratories v. Sandoz, Inc.,* 544 F.3d 1341; 89 USPQ2d 116 (Fed. Cir. 2008), the Federal Circuit stated as follows:

> In addressing the question of obviousness, a district judge is not to rely on hindsight, and must not pick and choose isolated elements from the prior art and combine them so as to yield the invention in question, if such a combination would not have been obvious at the time of the invention. The obviousness inquiry must guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue. *Id.* at 1349, citing *Dennison Mfg. Co. v. Panduit Corp.,* 475 U.S. 809, 106 S. Ct. 1578, 89 L. Ed. 2d 817 (1986); *Graham v. John Deere Co.,* 383 U.S. 1, 148 U.S.P.Q 459 (1966).

The Scope of the Prior Art

Radomsky

Radomsky teaches the use of various types of bone forming agents, for example, hyaluronic acid (HA) and a growth factor and a combined formulation of HA and a growth factor. Radomsky teaches that the growth factor can be fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth

factors (IGF) or transforming growth factor (TGF) (*see* col. 1, line 19 and lines 34-39). Radomsky teaches that the composition can be administered to the site where bone growth is desired. Radomsky does not teach any monoclonal antibody against TNF-α (*e.g.*, REMICADE® infliximab).

Binette

Binette centers on the use of genetically engineered chondrocytes capable of producing therapeutic agents. Essentially, Binette teaches the use of genetically engineered chondrocytes as a delivery system for a therapeutic agent based on the post-implantation survival advantages of the chondrocytes (*e.g.*, increased survival rates in harsh environments; no requirement of vascular support for survival; and no requirement to form an organized tissue, *etc*). Although Binette teaches that such chondrocytes can be used to treat bone disorders (osteoporosis) (*see* Binette at paragraph [0008]), Binette does not teach that a monoclonal antibody against TNF-α (*e.g.*, REMICADE® infliximab) can be used for treating osteoporosis. Binette merely teaches that REMICADE® infliximab can be used for treating rheumatoid arthritis, which Binette described as an autoimmune disease. In fact, Binette explicitly distinguishes a bone metabolic disorder, such as osteoporosis, from an autoimmune disorder, such as rheumatoid arthritis. (*compare* Binette, paragraph [0008] to paragraphs [0073] and [0076]).

Differences Between the Cited References and the Present Invention

Applicants' claims are directed to treating an uncoupled resorbing bone in a patient by administering to the patient a monoclonal antibody that inhibits TNF-α. Independent Claim 1 is directed to a method of therapeutically treating an uncoupled resorbing bone in a patient, comprising the steps of: administering an effective amount of a first formulation comprising a bone forming agent into the bone, and administering an effective amount of a second formulation comprising an anti-resorptive agent into the bone, wherein the anti-resorptive agent is a highly specific cytokine antagonist comprising *a monoclonal antibody that inhibits TNF-α.* Further, independent Claim 21 is directed to a method of treating osteoporosis in a patient, comprising administering an effective amount of a formulation comprising an effective amount of a highly specific cytokine antagonist into an uncoupled resorbing bone, wherein the highly specific cytokine antagonist comprises *a monoclonal antibody that inhibits TNF-α.*

As discussed above, neither Radomsky nor Binette teaches that a monoclonal antibody against TNF-α (*e.g.*, REMICADE® infliximab) can be used for treating an uncoupled resorbing bone disorder such as osteoporosis.

A Prima Facie Case of Obviousness Has Not Been Established

A *prima facie* case of obviousness has not been established because one of ordinary skill in the art would not have been motivated to combine the teachings of Radomsky with the teachings of Binette, or to modify the teachings of Radomsky and Binette, to arrive at the present invention.

According to the Federal Circuit, in the chemical arts, it is necessary to identify some reason that would have led one of ordinary skill to combine teachings or modify a known compound in a particular manner to establish *prima facie* obviousness. *See Takeda*, 83 USPQ2d at 1174 (2007). Neither Radomsky nor Binette teaches or provides a reasonable inference that a monoclonal antibody that inhibits TNF-α (*e.g.*, REMICADE® infliximab) can be useful for treating an uncoupled resorbing bone in a combinatorial therapy. Nor does the Office Action explains why one of ordinary skill in the art would have selected a monoclonal antibody such as REMICADE® infliximab in conjunction with a BFA for treating an uncoupled resorbing bone.

As noted above, Radomsky centers on the use of BFAs to treat osteoporosis and is silent regarding the use of a monoclonal antibody that inhibits TNF-α. Binette merely teaches the use of chondrocytes as a delivery system where the chondrocytes are genetically engineered to produce a desired biological agent selected from numerous known candidates at the time of the invention, including REMICADE® infliximab. Binette teaches various growth factors which are also mentioned in Radomsky for promoting bone growth in treating bone disease (*e.g.*, FGF, EGF, TGF-β, PDGF, GDF/MP-52, IGF; *see* Binette, paragraphs [0052] and [0066]). The use of REMICADE® infliximab is, however, clearly limited to the treatment of rheumatoid arthritis, (*see* Binette at page 7, paragraphs [0076] and [0077]), which Binette explicitly distinguishes from a bone disorder such as osteoporosis. Therefore, one of ordinary skill in the art would not have reasonably inferred from the teachings of Binette that REMICADE® infliximab could be useful for treating osteoporosis. Radomsky simply does not teach the use of any anti-resorptive

agent (*e.g.*, a monoclonal antibody or TNF-α) as acknowledged in the Office Action (*see* the Office Action at page 3).

The relevance of the teachings of Radomsky directed to BFAs and the teachings of Binette regarding the use of a TNF-α antagonist is far too tenuous to motivate one of ordinary skill in the art to combine the teachings to arrive at the present invention. Because Binette describes the use of REMICADE® infliximab in connection with treatment of rheumatoid arthritis, one of ordinary skill in the art would not have been motivated to particularly select REMICADE® infliximab (a monoclonal antibody against TNF-α) for treating an uncoupled resorbing bone as in osteoporosis. In fact, at the time of the invention, REMICADE® infliximab was a well-known medicament for the treatment of autoimmune diseases such as rheumatoid arthritis, ulcerative colitis, psoriasis or Crohn's disease, but not for osteoporosis, as evidenced by the teachings of Binette. The teachings of Binette directed to osteoporosis in paragraph [0008] are not related to the use of REMICADE® infliximab. As noted above, Binette teaches various growth factors which are also mentioned in Radomsky for promoting bone growth. As evidenced in paragraphs [0076] and [0077], the teachings of Binette regarding the use of REMICADE® infliximab is limited to its well-known conventional use for the treatment of rheumatoid arthritis, an autoimmune disease, as distinguished from osteoporosis. The mere fact that two elements (*i.e.*, a monoclonal antibody against TNF-α and osteoporosis) are disclosed in one reference, but in unrelated aspects, would not have led one of ordinary skill to combine the disclosed aspects, unless there is an identifiable reason to do so. *See Takeda*, 83 USPQ2d at 1174 (2007). In fact, in this case, Binette taught REMICADE® infliximab as a treatment for rheumatoid arthritis, but not for osteoporosis, and distinguished the two diseases from each other. Thus, one of ordinary skill in the art would have reasonably understood that Binette did not consider REMICADE® infliximab as a treatment for osteoporosis. Nor does the Office Action offer any other reasoning as to why one of ordinary skill in the art would have been motivated to choose a monoclonal antibody against TNF-α in the claimed invention. Thus, the relevance of Radomsky directed to the use of BFA and Binette directed to the use of REMICADE® infliximab is far too attenuated to motivate one of ordinary skill in the art to combine the teachings to arrive at the present invention.

Further, the chondrocytes described in Binette are solely used as a delivery system, and not for promoting bone growth or treating an uncoupled resorbing bone. Binette states that: "The chondrocytes do not perform the function of cartilage tissue (enabling friction-free articulation), and thus they are not used for tissue repair or construction with a tissue engineered construct" (Binette, page 6, paragraph [0062]). Rather, as noted above, Binette teaches that the chondrocytes offer physical characteristics highly desirable for a delivery system. Accordingly, the aspects relating to the use of chondrocytes in Binette do not establish any inference that the chondrocytes themselves have a therapeutic effect on osteoporotic bones. Thus, neither Radomsky nor Binette provides a reasonable inference that the use of a monoclonal antibody against TNF-α such as REMICADE® infliximab is useful for treating an uncoupled resorbing bone.

In sum, despite the Federal Circuit's statement that, to establish *prima facie* obviousness, it is necessary to identify some reason that would have led one of ordinary skill to combine teachings or modify a known compound in a particular manner, neither the Office Action nor the combination of the references of record provide a reasonable inference or any explanation as to why one would have been motivated to use a monoclonal antibody against TNF-α (*e.g.*, REMICADE® infliximab) for treating an uncoupled resorbing bone as claimed in Applicants' invention. A *prima facie* case of obviousness, therefore, has not been established.

The Present Invention Is Not Obvious Under the "Obvious To Try" Rationale

The present invention was not an obvious design choice to try in a combinatorial therapy for treating an uncoupled resorbing bone because there was not a finite number of identified predictable solutions to the recognized need for problem. *See KSR Int'l Co.*, 127 S. Ct. 1727 (2007). The known options in the prior art for treating an uncoupled resorbing bone were not finite, identified and predictable as indicated by the teachings of Radomsky. Radomsky provides numerous agents for promoting bone growth (*e.g.,* hyaluronic acid (HA), bFGF, EGF, PDGF, TGF-β, BMP1-12, GDF1-12, dpp, 60A, BIP, OF, *etc.*; *see* Radomsky, col. 1, lines 24-39). Families of bisphosphonates, pentosan polysulfates and calcitonins were also well known at the time of the invention to be useful for treating osteoporosis, as well as various types of hormone therapy (*see* Cullis-Hill, U.S. Patent No. 6,593,310 which was previously cited in the Office

Action dated May 20, 2009). It is noted that Binette uses REMICADE® infliximab for treating rheumatoid arthritis which Binette distinguishes from bone disorders like osteoporosis. A monoclonal antibody against TNF-α, therefore, was not one of the predictable options or solutions that a skilled artisan could have easily chosen or foreseen to be useful in treating an uncoupled resorbing bone and there was no finite number of identified predictable solutions to treat an uncoupled resorbing bone. *See KSR Int'l Co.*, 127 S. Ct. 1727 (2007).

In summary, one of ordinary skill in the art would not have been motivated to choose REMICADE® infliximab as an antiresorptive agent (ARA) in combination with a BFA to arrive at the claimed methods because, absent impermissible hindsight, there is no inference of success that can be drawn from the teachings of the reference of record or the general knowledge available in the art regarding the use of a monoclonal antibody against TNF-α in treating an uncoupled resorbing bone -- particularly in conjunction with a BFA. Nor was the present invention an obvious design choice to try for treating an uncoupled resorbing bone. Therefore, a *prima facie* case of obviousness has not been established for Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 over Radomsky in view of Binette. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 4 and 24 Under 35 U.S.C. § 103(a)

Claims 4 and 24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky in view of Binette and further in view of Boyle *et al.* ("Osteoprotegerin," U.S. Publication No.: 2003/0207827; hereinafter, "Boyle"). Current Claims 4 and 24 are directed to methods of treating an uncoupled resorbing bone or osteoporosis in a menopausal female patient.

The Office Action states that: "It would have been obvious to one of ordinary skill at the time of instant invention to utilize the bone forming agent and [REMICADE® infliximab] to post menopausal women as a patient motivated by the teachings of Boyle et al. teaching the administration of [antiresorptive] agents for treatment of osteoporosis in post menopausal women." (Office Action at page 6, first full paragraph).

The teachings of Radomsky and Binette are discussed in detail above. Specifically, Radomsky teaches the use of BFAs (*e.g.*, HA and growth factors) for promoting bone growth. Binette teaches the use of genetically engineered chondrocytes capable of, for example,

expressing REMICADE® infliximab for treating rheumatoid arthritis. For the reasons stated above, one of ordinary skill in the art at the time of the invention would not have been motivated to combine these references to practice applicants' claimed invention with a reasonable expectation of success.

The entire teachings of Boyle are directed to "osteoprotegerin" (OPG), a novel secreted receptor which belongs to the TNF receptor superfamily. Boyle states that OPG plays a role in promoting bone accumulation and can be used to treat bone loss diseases, such as osteoporosis in a menopausal patient (Boyle, page 1, paragraphs [0001] and [0006]). Boyle does not teach that OPG functions via TNF-α. Nor does it teach that an antibody that inhibits TNF-α is useful for treating osteoporosis as in the present invention.

Boyle is relied upon by the Examiner for its teachings directed to the use of OPG for treating osteoporosis in post menopausal women. OPG is a receptor (peptide), not an antibody. In its three-dimensional structure modeling, Boyle demonstrates a co-crystallization of OPG protein complexed with TNF-β in order to illustrate the interaction of OPG with its potential ligand as previously discussed. Notably, Boyle makes no reference as to whether OPG binds to or inhibits TNF-α or as to whether the biological effect of OPG is via TNF-α. Boyle's teachings directed to OPG simply do not compensate for the deficiencies in Radomsky and Binette, particularly in view of the fact that Claims 4 and 24 depend from claims which recite that the ARA is a monoclonal antibody against TNF-α such as REMICADE® infliximab. Simply, Boyle does not teach a monoclonal antibody against TNF-α for treating osteoporosis.

Therefore, the combined teachings of Radomsky, Binette and Boyle do not render Claims 4 and 24 obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 60 Under 35 U.S.C. § 103(a)

Claim 60 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radomsky in view of Binette and further in view of Trieu *et al.* (U.S. Publication No.: 2002/0026244; hereinafter, "Trieu"). The Office Action states that: "It would have been obvious to the one of ordinary skill in the art at the time the invention was made to incorporate highly specific cytokine antagonist such as [REMICADE® infliximab] as taught by '595 to the teachings of Trieu since the reference teaches advantage of the same in treating osteoporosis with

bone morphogenetic protein etc. One skilled in the art would have been motivated to administer into the bone the formulation comprising the bone forming agent and [REMICADE® infliximab] because Trieu et al. successfully teach local administration of implants/drug in between bones in order to treat osteoporosis" (the Office Action at page 7).

Applicants respectfully disagree. Instant Claim 60 is directed to administering an effective amount of a bone forming agent and an anti-resorptive agent into the vertebral body. The vertebral body is the spinal bone itself ("vertebra"). However, Trieu's teachings are directed to placing an implant in the spinal disc by: (1) removing the natural nucleus pulposus of the intervertebral disc; and (2) placing an implants in the space created by the removal of the nucleus pulposus, as the title of the Trieu reference indicates (*i.e.*, "*Intervertebral disc nucleus implants and methods*"). Thus, Trieu's teachings are directed to placing an implant in the intervertebral disc, not *into the vertebral bone*. In contrast, the claimed invention is directed to inserting a device into the spinal bone(s) ("vertebral body"). Unlike the statement in the Office Action, Trieu does not teach or motivate one of the ordinary skill in the art to administer a therapeutic agent into the vertebral body as in Claim 60.

The combined teachings of the references do not provide any inference regarding the use of a monoclonal antibody against TNF-α for treating an osteoporotic patient. Simply, the teachings of Trieu do not compensate for the deficiencies in Radomsky and Binette, particularly in view of their deficiencies regarding the use of a monoclonal antibody against TNF-α for treating an uncoupled resorbing bone. Thus, these references would not have motivated one of ordinary skill in the art at the time of the invention to implement a monoclonal antibody against TNF-α for treating an uncoupled resorbing bone as elaborated above.

Finally, Applicants note that, in the previous Amendment filed before the Office on October 20, 2009, Claim 60 was amended to delete the elements directed to: (1) removal of a portion of the disc; and (2) insertion of a spinal implant into the disc space. As amended, Claim 60 no longer recites the elements relating to the teachings of Trieu. Thus, this amendment to Claim 60 should have rendered the rejection moot and placed Claim 60 in condition for reconsideration. However, the comparison to Trieu in the rejection has been repeated verbatim in the present Office Action with no reference to the claim amendment and related discussion in

that Amendment. Applicants respectfully request Claim 60 be properly reconsidered in light of the amendment made on October 20, 2009.

Specifically, the teachings of Trieu are limited to a method of administering a formulation from an implant placed in the nucleus pulposus in between two vertebral bones. The Office Action characterizes this type of administration as "local administration in between bones" (the Office Action at page 7; emphasis added). Administration by releasing a formulation from an implant placed in between two bones (*i.e.*, two vertebrae) is not equivalent to, nor does it suggest, administration which involves delivering the formulation into the bone as in present Claim 60 due to the difference in mechanical and physiological responses. Moreover, Trieu is focused on a condition other than osteoporosis.

In sum, one would not have been motivated to modify the teachings of Trieu to treat an osteoporotic patient by inserting an implant *into* the bone. None of these references of record teaches or provides a reasonable inference of success that a monoclonal antibody against TNF-α is useful for treating osteoporotic bones as discussed above. Therefore, a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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